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Clinical Investigation

CLINICAL INVESTIGATION

Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial

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Abstract

Background: Postpartum haemorrhage (PPH) can be exacerbated by haemostatic failure. We hypothesized that early fibrinogen replacement, guided by viscoelastometric testing, reduces blood product usage and bleed size.
Methods: Women with PPH 1000–1500 ml were enrolled. If Fibtem A5 was ≤15 mm and bleeding continued, subjects were randomized to fibrinogen concentrate or placebo. The primary outcome compared the number of units of red blood cells, plasma, cryoprecipitate and platelets transfused.
Results: Of 663 women enrolled 55 were randomized. The adjusted incidence rate ratio (IRR) (95% CI) for the number of allogeneic units transfused in the fibrinogen group compared with placebo was 0.72 (0.3–1.7), P=0.45. In pre-specified subgroup analyses, subjects who had a Fibtem A5 ≤12 mm at the time of randomization and who received fibrinogen concentrate received a median (25th–75th centile) of 1 (0–4.5) unit of allogeneic blood products and had an additional 300 (100–350) ml blood loss whereas those who received placebo also received 3 (0–6) units of allogeneic blood products and had 700 (200–1550) ml additional blood loss; these differences were not statistically significantly different. There was one thrombotic event in each group.
Conclusions: Infusion of fibrinogen concentrate triggered by Fibtem A5 ≤15 mm did not improve outcomes in PPH. Pre-specified subgroup analyses suggest that fibrinogen replacement is not required if the Fibtem A5 is > 12 mm or Clauss fibrinogen >2 g litre^{-1}, but an effect below these levels cannot be excluded. The raised fibrinogen at term appears to be a physiological buffer rather than required for haemostasis.

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Key words: fibrinogen; postpartum haemorrhage; viscoelastometry

Editor's key points

- Severe postpartum haemorrhage can be exacerbated by coagulopathy, but the role of early targeted fibrinogen replacement is unknown.
- Women with severe postpartum haemorrhage and reduced fibrinogen assessed by viscoelastometry were randomized to receive fibrinogen concentrate or placebo.
- Fibrinogen replacement for moderate reduction in fibrinogen did not reduce allogeneic blood product transfusion or blood loss in postpartum haemorrhage.

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality and severe maternal morbidity worldwide,[1 2] and its incidence is increasing in many countries.[3–6] Bleeding is precipitated by obstetric causes but can be exacerbated by haemostatic impairment.[7 8] At term, the haemostatic system is prothrombotic[7 9] with fibrinogen concentrations of 4–6 g litre^{-1} compared with 2–4 g litre^{-1} in the non-pregnant population.[10 11] Fibrinogen decreases earlier than other coagulation factors during PPH,[12 13] suggesting a potentially important role in haemostasis. Fibrinogen <3 g litre^{-1}, measured early during PPH, is associated with progression to massive haemorrhage, red blood cell (RBC) and fresh frozen plasma (FFP) transfusion, invasive procedures and level 2/3 admission. Fibrinogen >4 g litre^{-1} is less often associated with progression of bleeding.[12 14–17] During PPH, it is unknown whether fibrinogen should be maintained at a level that is normal for term (>4 g litre^{-1}), above the non-pregnant range (>2 g litre^{-1}) or an intermediate level (3 g litre^{-1}).

The clinical utility of laboratory fibrinogen to predict progression of PPH is limited because results take 60–90 min to become available.[18] A point-of-care viscoelastometric test, Rotem® (Tem International, Munich, Germany) provides a Fibtem A5 result within 10 min. Fibtem correlates with laboratory fibrinogen during PPH,[19] and in an observational study A5 ≤15 mm was usually associated with progression of PPH whereas A5 >22 mm was not.[14] To study the appropriate level of fibrinogen-related haemostasis required during PPH, we investigated whether fibrinogen replacement improved outcomes if Fibtem A5 was ≤15 mm (fibrinogen about 3 g litre^{-1}).

Methods

This was a multicentre, randomized, double-blind, placebo-controlled trial set in teaching hospital obstetric units. It was approved by the Edinburgh Multicentre Research Ethics Committee (13/SS/0008). Trial registration: ISRCTN46295339 (http://www.isrctn.com/ISRCTN46295339, last accessed 5 July 2017), EudraCT 2012-005511-11 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-005511-11, last accessed 5 July 2017). The protocol has been published.[20]

Women aged ≥18 yr and ≥24 weeks gestation who had ongoing major PPH (1000–1500 ml blood loss) could be enrolled. Women were excluded if they declined transfusion, had placenta accreta diagnosed antenatally, had undergone an invasive procedure to control bleeding or if there was clinical suspicion of amniotic fluid embolus. Detailed inclusion and exclusion criteria have been published.[20] Women received written information in their maternity notes. Verbal consent was sought at enrolment and confirmed in writing when the woman had recovered from the bleed. At study entry, a Fibtem was performed in the delivery suite and samples were sent to the laboratory for full blood count, Clauss fibrinogen, prothrombin time (PT) and activated partial thromboplastin time (aPTT). Blood loss was measured gravimetrically as described.[21] Local standard treatment was instituted except that FFP was not infused if the Fibtem A5 was >15 mm.

Fibtem was repeated after each additional 500 ml blood loss or for clinical concern. If the A5 was ≤15 mm, the baby delivered and bleeding ongoing the woman was randomized. Randomization and blinding procedures are published.[20] Study medication was fibrinogen concentrate (Riastap, Marburg, Germany) or placebo (normal saline, Fresenius Kabi AG, Homburg, Germany). The study design is shown in the Supplementary data, Figure S1. The method for mixing and blinding the fibrinogen and placebo using an opaque cover is published.[22] Vials contained either 1 g of fibrinogen in 50 ml of water or 50 ml of normal saline. The dose of fibrinogen or placebo infused was calculated according to:

$$(number\ of\ vials) = (23 - Fibtem\ A5) \times ideal\ body\ weight\ for\ height/140$$

rounded to the nearest 1 g. Investigators had a chart with precalculated doses.[20] The aim was to increase Fibtem A5 to >22 mm in the fibrinogen arm. At randomization 1 g of tranexamic acid was infused if not already given and 4 units of FFP ordered. Some or all of the FFP was infused when it arrived if bleeding was ongoing or there had been an additional 500 ml of blood loss since randomization. If bleeding stopped further FFP could be withheld. Fibtem and coagulation screens were performed 15 min after study medication. These results were not available to the treating clinicians until after the decision to give FFP had been made. Subsequent treatment was at the discretion of treating clinicians. Women were contacted 6 weeks after randomization to record establishment of breastfeeding and adverse events including thrombosis.

Information was collected through an electronic case report form.[20] The primary endpoint was the number of allogeneic blood products (RBC, FFP, cryoprecipitate, platelets) infused after study medication until hospital discharge between the two randomized arms. Secondary endpoints were: measured blood loss, numbers of units of RBC, FFP, cryoprecipitate, and platelet transfusion within the first 24 h, cell salvage, change in Fibtem and Clauss fibrinogen, invasive procedures and initiation of breastfeeding. Safety endpoints were thrombosis to 6 weeks, level 2 and 3 admission and length of hospital stay.

Statistical analysis

Based on data collected in a previous study with the same entry criteria,[14] we calculated that 54 women were needed to provide

80% power at the two-sided 5% level to detect a difference of 3.3 total allogeneic units between groups. We allowed for a 10% dropout rate and inflated the recruitment target to 60. Full details of the sample size calculation are published.[20]

Analyses are intention-to-treat without imputation, with outcomes compared between groups using mixed-effects two-level regression models to adjust for site and allow for clustering. Akaike's Information Criterion was used to select the best fitting model. Models were adjusted for two pre-specified confounders: Caesarean section and placental abruption. Where data were skewed, transformations were performed.

For binary outcomes, a logistic model was used and results presented as adjusted odds ratios (ORs) alongside 95% confidence intervals (CIs). For continuous outcomes, a linear regression model was fitted and results presented as difference in adjusted means (fibrinogen minus placebo) alongside 95% CIs. Count data were analysed using Poisson multilevel or negative binomial models if over-dispersion was evident and presented as incident rate ratios (IRRs). The IRR compares the rate of events (e.g. total transfused units divided by the number of patients) as a ratio of fibrinogen to placebo. Where distributions were skewed, a natural log transformation was performed for regression analysis.

Pre-specified subgroup analyses were conducted on the primary outcome by inclusion of an interaction term in the model. As the trial is powered to detect overall differences between the groups rather than interactions of this kind, the results of these exploratory analyses are presented using CIs as well as *P*-values. Subgroups were:

- Fibtem A5 at randomization $\leq$12 or $>$12 mm
- Fibrinogen at randomization $<$2 or $\geq$2 g L^{-1}
- Caesarean section *vs* vaginal birth
- Platelets $<$100 or $\geq$100 x 10^{9} litre^{-1} at randomization

Analyses were performed by R.C.-J. using SPSS version 20 (IBM SPSS Inc, Chicago, USA) and Stata version 13 (StataCorp LLC, Texas, USA).

Results

Between June 29, 2013 and November 26, 2015, 663 women from six centres gave informed consent for study inclusion (Fig. 1). In total, 57/663 (8.7%) women were randomized. Two of the 57 women were later found to be ineligible for randomization (in one case the baby was not delivered and in the other case an invasive radiological procedure had been performed before study entry); therefore, 55 women were analysed. The 605 women enrolled, but not randomized, has been reported elsewhere.

Baseline characteristics were balanced between trial groups (Table 1). The median (25th–75th centile) measured blood loss was 1450 (1200–1800) ml at enrolment and 1950 (1500–2285) ml when study medication was infused. Fibtem and fibrinogen at time of study medication were similar in the two arms (Table 2).

There were no missing data for the primary outcome. Women in the fibrinogen arm received 58 units (mean transfusion rate of 2.07) of allogeneic blood products compared with 75 units (mean transfusion rate of 2.78) in the placebo arm, median (25th–75th centile, range) 1.0 (0–2.75, 0–15) for fibrinogen and 1.0 (0–4, 0–23) for placebo. There was no evidence of a treatment effect [adjusted IRR 0.72 (95% CI 0.30–1.70), P=0.45]. There was no evidence of clustering between sites or in women who had a Caesarean section (intra-cluster correlation coefficient = –0.031).

Women in the fibrinogen arm received 37 units of RBC compared with 38 units in the placebo arm. The difference in total allogeneic infusions was therefore due almost entirely to FFP where 6/28 (21%) women randomized to fibrinogen received a total of 18 units, and 8/27 (30%) women randomized to placebo received 33 units IRR 0.53 (0.13–2.16) (Table 3). Blood loss after study medication was similar between arms (Table 3).

An invasive procedure before study medication was performed in 11/28 (39%) and 9/27 (33%) women in the fibrinogen and placebo groups, respectively. After study medication, invasive procedures in the fibrinogen and placebo arms were similar (Table 3 and supplementary Table 1). There was a right pulmonary artery thrombosis in the fibrinogen arm and a right ovarian vein thrombosis in the placebo arm.

Changes in Fibtem, fibrinogen, PT and aPPT following study medication are shown in Table 2. There was a difference in fibrinogen, Fibtem A5 and aPPT between the arms at 15 min but not at 24 h. The Fibtem A5 increased to $>$22 mm in 2/28 (7.1%) women in the fibrinogen group.

Subgroup analyses

Pre-specified subgroup analyses for the primary outcome and *post hoc* subgroup analyses for blood loss and time on level 2/3 care are shown in Table 4. At randomization, there were 28 women with Fibtem A5 $\leq$12 mm and 27 women $>$12 mm. Blood loss at randomization was similar, median (25th–75th centile) 2000 (1650–2390) and 2000 (1670–2370) in the $\leq$12 mm and $>$12 mm groups, respectively. Outcomes were indistinguishable between the fibrinogen and placebo groups in women randomized with a Fibtem A5 $>$12 mm. Women with A5 $\leq$12 mm at randomization who received fibrinogen had fewer allogeneic blood products, less bleeding (Fig. 2) and less time in level 2/3 care. The overall interaction between treatment arm and Fibtem A5 was not significant for any outcome.

At randomization, 39 women had a fibrinogen $>$2 g litre^{-1}, 21 received fibrinogen and 18 received placebo. Blood loss at randomization was median (25th–75th centile) 2350 (2000–2080) and 1950 (1630–2290) in the $<$2 g litre^{-1} and $\geq$2 g litre^{-1} groups, respectively. In the women randomized with a fibrinogen $>$2 g litre^{-1}, outcomes were indistinguishable between arms (Table 4 and Fig. 2). Seven women had fibrinogen $<$2 g litre^{-1} at randomization, outcomes are shown in Table 4 and Figure 2. The overall interaction between treatment arm and fibrinogen at randomization was not significant for any outcome.

Median fibrinogen at the time of study medication infusion was 2.5 g litre^{-1}. *Post hoc* analysis was performed, investigating women randomized with a fibrinogen $\leq$2.5 (n=24) or $>$2.5 g litre^{-1} (n=22). In women randomized with a fibrinogen $\leq$2.5 g litre^{-1}, the total allogeneic blood products infused was median (25th–75th centile) 2 (1–5) units in the fibrinogen arm and 3 (0–5.5) units in the placebo arm. Women randomized with a fibrinogen $>$2.5 g litre^{-1} were transfused 0 (0–0) total allogeneic units in both the fibrinogen and placebo arms. Blood loss after study medication in women with fibrinogen $\leq$2.5 g litre^{-1} was 300 (165–673) ml in the fibrinogen arm and 850 (315–1845) ml with placebo. In women randomized with a fibrinogen $>$2.5 g litre^{-1}, blood loss was 200 (55–1540) ml and 150 (28–300) ml in the fibrinogen and placebo groups, respectively. When scatter plots of blood loss and fibrinogen are examined by trial arm (Fig. 2), there appears to be a differential relationship, but when a linear model was fitted to transformed (log plus one) data (due to skewed blood loss data), their interaction was not statistically significant (difference in log + 1 means=1.23, 95% CI: –0.45 to 2.90).

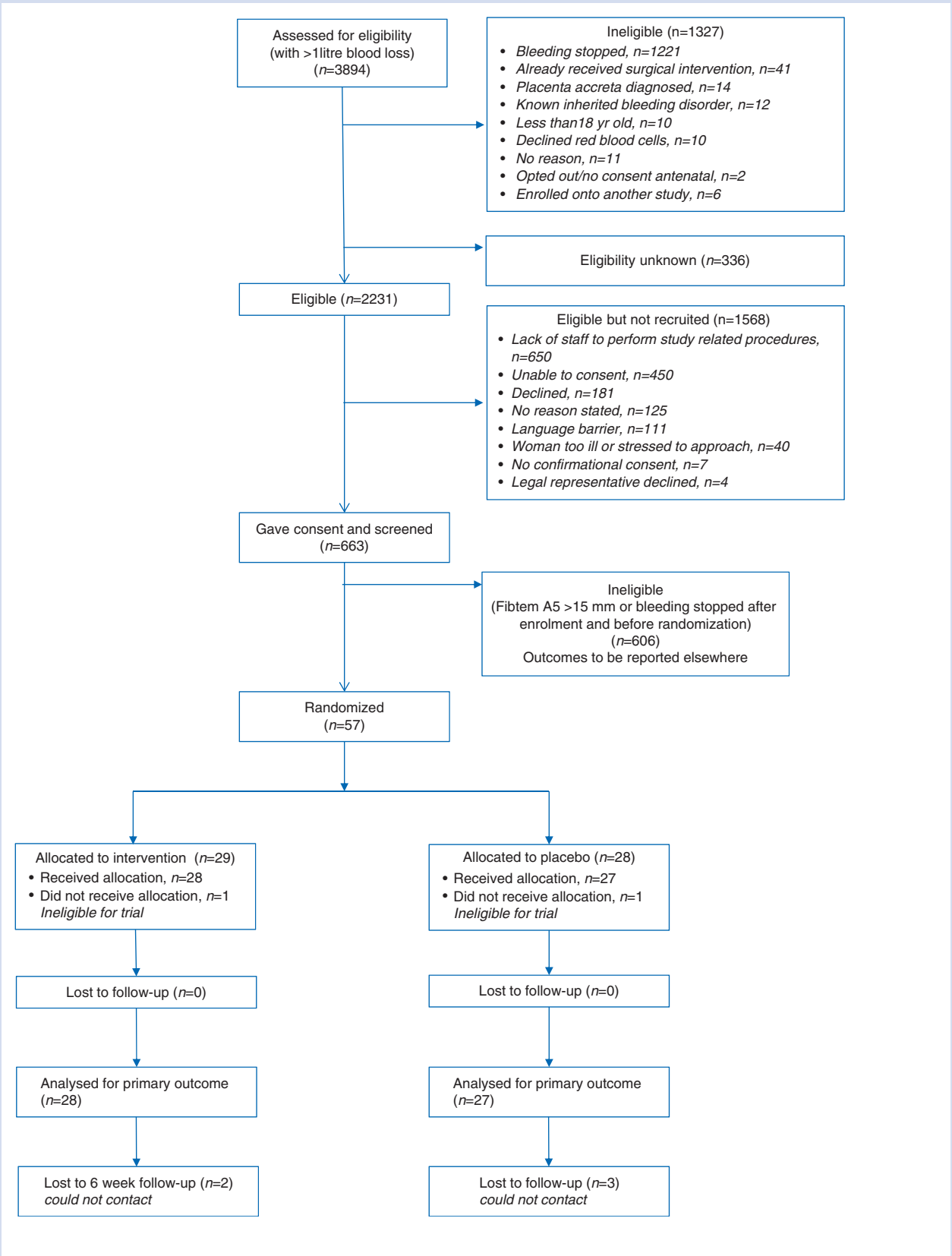

Fig 1 Consort diagram.

Table 1 Baseline maternal characteristics at study entry by trial arm. *Women may have had more than one cause of bleeding. †For multiple pregnancies, the most invasive mode is taken

Variable	Fibrinogen (*n*=28)	Placebo (*n*=27)
Demographics		
Age at recruitment (yr), mean (range)	30.8 (19–42)	33.5 (20–48)
Ethnicity, *n* (%)		
White	17 (60.7)	22 (81.5)
Other	11 (39.3)	5 (18.5)
BMI at booking, mean (SD)	26.4 (5.40)	25.3 (4.57)
Missing *n*	0	1
Previous Caesarean section, *n* (%)	9 (32.1)	9 (33.3)
Pre-eclampsia during this pregnancy, *n* (%)	3 (10.7)	5 (18.5)
Past history of postpartum haemorrhage, *n* (%)	5 (17.9)	6 (23.1)
Delivery		
Onset of labour, *n* (%)		
Spontaneous	9 (32.1)	9 (33.3)
Induced	4 (14.3)	7 (25.9)
No labour	15 (53.6)	11 (40.7)
Multiple gestation, *n* (%)		
Singleton	24 (85.7)	25 (92.6)
Twins	4 (14)	2 (7.4)
Reported causes of postpartum haemorrhage*, *n* (%)		
Uterine atony	23 (82.1)	16 (59.3)
Surgical bleeding	9 (32.1)	10 (37.0)
Trauma	6 (21.4)	4 (14.8)
Retained placenta	1 (3.6)	5 (18.5)
Placental abruption	2 (7.1)	3 (11.1)
Placental praevia	1 (3.6)	2 (7.4)
Undiagnosed placenta accrete	0 (0)	1 (3.7)
Mode of delivery†, *n* (%)		
Spontaneous vaginal	7 (25)	6 (22.2)
Instrumental vaginal	3 (10.7)	4 (14.8)
Elective Caesarean section	10 (35.7)	9 (33.3)
Non-elective Caesarean section	8 (28.6)	8 (29.6)
Blood loss		
Estimated blood loss at study entry (ml), median (25th–75th centiles)	1400 (1200–1575)	1500 (1000–2000)
Measured blood loss at administration of study medication (ml), median (25th–75th centiles)	1950 (1500–2280)	2000 (1700–2500)
Haemoglobin at study entry (g litre^{-1}), median (25th–75th centiles)	94.5 (86.3–108.8)	101 (73.0–108.0)
Time (min) from Fibtem triggering randomization to administration of study medication, median (25th–75th centiles)	24 (20–33)	26 (18–40)
Interventions		
Patients receiving at least one invasive procedure after study entry and prior to administration of study medication, *n* (%)	11 (39.3)	9 (33.3)
Crystalloid transfusion prior to administration of study medication (ml), median (25th–75th centiles)	2000 (2000–3375)	3000 (1875–4000)
Missing	0	1
Colloid transfusion prior to administration of study medication (ml), median (25th–75th centiles)	500 (0–500)	500 (500–1000)
Missing	1	2
Patients transfused red blood cells prior to administration of study medication, *n* (%), median units (25th–75th centiles)	8 (28.6) 0 (0–3)	9 (33.3) 0 (0–1.75)
Patients transfused fresh frozen plasma prior to administration of study medication, *n* (%)	0 (0.0)	0 (0.0)
Patients transfused platelets prior to administration of study medication, *n* (%)	0 (0.0)	2 (7.4)
Patients transfused cryoprecipitate prior to administration of study medication, *n* (%)	0 (0.0)	0 (0.0)

Discussion

Early infusion of fibrinogen concentrate in women experiencing moderate to severe PPH who had a Fibtem A5 ≤15 mm did not lead to a statistically significant reduction in transfusion requirements or blood loss. Pre-specified subgroup analyses suggested that a Fibtem A5 >12 mm or fibrinogen >2 g litre^{-1} are adequate for haemostasis and fibrinogen replacement is not necessary. An effect of fibrinogen infusion on blood product usage and bleed size at a Fibtem A5 ≤12 mm or Clauss fibrinogen <2.5 g litre^{-1} could not be excluded and should be investigated further.

Studies have shown that fibrinogen <3 g litre^{-1} or Fibtem A5 ≤15 mm, measured early during a PPH, is associated with progression to severe bleeding and the need for

Table 2 Haematological parameters over time (study entry, prior to randomization, 15 min and 24 h after study medication). *Adjusted for value prior to randomization. The median (25th–75th centile) number of vials of study medication infused was 3 (3–4) in the fibrinogen group and 4 (3–5) in the placebo group. PT, prothrombin time; aPTT, activated partial thromboplastin time

	Fibrinogen (n=28)	Placebo (n=27)	Adjusted* difference in means (95% CI)	P-value
Fibtem A5 (mm), mean (SD)				
Study entry	13.9 (2.6)	13.2 (4.0)	–	–
Prior to randomization	12.5 (2.2)	11.2 (2.7)	–	–
15 min after study medication	16.8 (3.8)	10.5 (3.6)	5.6 (3.5–7.7)	<0.001
24 h after study medication	20.8 (4.2)	17.8 (3.6)	2.2 (−0.02 to 4.4)	0.052
Clauss fibrinogen (g litre^{-1}), mean (SD)				
Study entry	2.6 (0.5)	2.9 (0.6)	–	–
Prior to randomization	2.6 (0.7)	2.6 (0.6)	–	–
15 min after study medication	3.2 (0.9)	2.3 (0.7)	0.9 (0.5–1.3)	<0.001
24 h after study medication	4.1 (0.8)	4.0 (0.9)	−0.02 (−0.5 to 0.5)	0.950
PT (s), mean (SD)				
Study entry	11.8 (2.1)	11.3 (1.6)	–	–
Prior to randomization	12.1 (2.1)	11.6 (1.8)	–	–
15 min after study medication	12.4 (2.1)	12.0 (2.0)	−0.2 (−0.8 to 0.2)	0.332
24 h after study medication	11.9 (2.4)	11.5 (1.4)	0.1 (−0.7 to 1.1)	0.735
aPTT (s), mean (SD)				
Study entry	27.0 (5.0)	26.2 (5.0)	–	–
Prior to randomization	28.4 (5.0)	27.2 (7.4)	–	–
15 min after study medication	28.8 (4.7)	30.5 (7.0)	−3.9 (−7.4 to − 0.4)	0.029
24 h after study medication	30.5 (4.6)	30.1 (4.0)	−0.1 (−2.2 to 1.9)	0.892

blood transfusion.[12 14–17] Our study investigated whether early correction of Fibtem/fibrinogen at these levels would improve outcomes. The results show that 15 mm is too high as an interventional trigger. Subgroup analyses suggest that A5 >12 mm or fibrinogen >2 g litre^{-1} is adequate for haemostasis during PPH and that fibrinogen replacement is not necessary.

These conclusions build on a previous double-blind randomized controlled trial in which 2 g of fibrinogen concentrate or placebo was infused after 1500 ml blood loss. There were no differences in any outcomes measured.[23] It was established retrospectively that the fibrinogen level when study drug was infused was mean (SD) 4.5 (1.1) g litre^{-1}, confirming that this level of fibrinogen is adequate for haemostasis during PPH and suggesting that a non-targeted, empirical approach to fibrinogen replacement is unlikely to be an optimal and cost-effective strategy.

An observational, non-randomized, open-label study described women with moderate PPH and a Fibtem A5 <7 or <12 mm with severe bleeding, (fibrinogen about 1.2 and 2.2 g litre^{-1}, respectively) who were infused 3 g fibrinogen concentrate that could be repeated if required. Compared with formulaic replacement in the ratios RBC:FFP:platelets 4:4:1, fewer women required >5 units of RBCs and transfusion-associated circulatory overload and intensive care unit admissions decreased.[24 25] Our study also suggests that a fibrinogen intervention trigger of about 2 g litre^{-1} is appropriate in severe PPH. In our study, blood product usage and bleeding decreased progressively in the fibrinogen arm compared with placebo as the fibrinogen level at randomization decreased suggesting a continuum effect.

The optimum fibrinogen level for intervention during PPH has been debated because fibrinogen at term (>4 g litre^{-1}) is higher than in the healthy non-pregnant population (2–4 g litre^{-1}). In our study, the target Fibtem A5 was 22 mm (fibrinogen about 4 g litre^{-1}) because this was associated with limited progression of bleeding in an observational study.[14] This target Fibtem was not achieved in most women, probably because fibrinogen continued to be consumed. This is unlikely to have affected the study outcome because there was no benefit from infusing fibrinogen if the level was above 2–2.5 g litre^{-1} and infusing fibrinogen concentrate when the fibrinogen is 4 g litre^{-1} has no effect.[23] Increased fibrinogen at term appears to be a physiological buffer rather than a requirement for haemostasis. Recently updated guidelines incorporate this finding.[26–28]

Fibrinogen <2 g litre^{-1} is uncommon during PPH. In a prospective observational study of 1951 women, fibrinogen concentration at admission was 5.3 g litre^{-1} and did not predict severe PPH.[29] In two consecutive cohorts of >24 000 women, of those with bleeds between 1000 and 2000 ml, a fibrinogen <2 g litre^{-1} was seen in 1–2 per 1000 deliveries.[13 14] The likelihood of a woman having a fibrinogen <2 g litre^{-1} depended on the cause and size of the bleed. It was uncommon at 1000–2000 ml blood loss due to atony and surgical bleeding,[14] but occurred in 60% of 6000 ml bleeds.[30] Fibrinogen <2 g litre^{-1} was more common with smaller bleeds associated with placental abruption and amniotic fluid embolus[14 29] due to consumptive coagulopathies.[31 32]

In our study, Fibtem A5 remained >15 mm and PT and aPTT normal in >90% of cases with bleeding controlled without haemostatic support. This suggests that early, formulaic and liberal use of FFP, based on practice extrapolated from major trauma, and recommended in some obstetric haemorrhage algorithms,[33 34] would result in many women with normal haemostasis receiving FFP, potentially contributing to adverse effects whilst not affecting haemostasis.

In this study, fewer women were randomized with a fibrinogen <2 g litre^{-1} than expected. This is probably because of challenges related to consenting women with severe bleeding and undertaking trial procedures whilst treating acutely ill women. This may have excluded women most likely to respond to

Table 3 Secondary study outcomes. *Effect estimates from the unadjusted model are displayed as site, Caesarean section and platelet count at the time of randomization had no effect on these study outcomes. †Odds ratio (OR) of the fibrinogen arm compared with placebo arm. An OR < 1 indicating a higher proportion in placebo compared with the fibrinogen and an OR > 1 indicating a higher proportion in the fibrinogen compared with the placebo. ‡Incidence rate ratio (IRR) of the fibrinogen arm compared with placebo arm. An IRR <1 indicating a higher incidence rate of transfusions in placebo compared with the fibrinogen arm and an IRR >1 indicating a higher incidence rate of transfusions in the fibrinogen arm compared with the placebo. ¶Data were transformed before modelling using log plus one transformation. §Data were log transformed due to skewed distribution. The estimate should be interpreted as a ratio of logs (fibrinogen:placebo) rather than a difference. ||Hazard ratio (HR) of the fibrinogen arm compared with placebo arm. A HR < 1 indicating a higher duration in the placebo compared with the fibrinogen arm and a HR > 1 indicating a higher duration in the fibrinogen arm compared with the placebo. NA, not analysed because of insufficient data for analysis in regression model; RBC, red blood cell; FFP, fresh frozen plasma

	Fibrinogen (*n*=28)	Placebo (*n*=27)	Unadjusted* treatment effect estimate (95% CI)	*P*-value
Allogeneic blood products transfused between study drug completion and date of discharge				
No allogenic products transfused, *n* (%)	13 (46.4)	12 (44.4)	0.92† (0.32–2.67)	0.88
RBC transfusions				
Total number	37	38		
Mean transfusion rate (total transfusions/*n*)	1.32	1.41	0.94‡ (0.44–2.02)	0.87
Median (25th–75th centile)	1 (0–2)	1 (0–2)		
Range	0–9	0–8		
No RBC transfused, *n* (%)	13 (46.4)	13 (48.1)		
FFP transfusions				
Total number	18	33		
Mean transfusion rate (total transfusions/*n*)	0.64	1.22	0.53‡ (0.13–2.16)	0.37
Median (25th–75th centile)	0 (0–0)	0 (0–2)		
Range	0–4	0–8		
No FFP transfused, *n* (%)	22 (78.6)	19 (70.4)		
Platelet transfusions				
Total number	2	3		
No platelets transfused, *n* (%)	27 (96.4)	24 (88.9)	NA	
Cryoprecipitate transfusions				
Total number	1	1		
No cryoprecipitate transfused, *n* (%)	27 (96.4)	26 (96.3)	NA	
Measured abnormal blood loss (ml):				
Within 24 h of study medication				
Median (25th–75th centile)	225 (100–341.25)	300 (60–800)	−0.25§ (−1.35 to 0.85)	0.66
Range	0–1465	0–3000		
Between study medication and date of discharge	As above	As above		
Invasive procedures after study medication, *n* (%)				
Within 24 h of study medication	4 (14.3)	5 (18.5)	0.73† (0.17–3.08)	0.67
Between study medication and date of discharge	5 (17.9)	5 (18.5)	0.96† (0.24–3.77)	0.95
Level 2 care				
Admitted to level 2 care, *n* (%)	27 (96.4)	24 (88.9)	3.38† (0.33–34.65)	0.31
Length of stay (h), median (25th–75th centile)	16.0 (12.0–25.0)	20.5 (10.5–28.5)	−0.03§ (−0.48 to 0.42)	0.90
Range	2–152	1.5–88		
Level 3 care				
Admitted to level 3 care, *n* (%)	(7.1)	2 (7.4)	−0.003† (−0.14 to 0.13)	0.97
Length of hospital stay (days)				
Median (25th–75th centile)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	0.23§ (−0.07 to 0.52)	0.13
Mean (SD)	2.89 (1.05)	4.50 (4.37)		
Range	1–23	1–6		
Breastfeeding at 6 week follow-up				
Ever breastfed, *n* (%)	17 (68.0)	19 (79.2)	0.56† (0.15–2.04)	0.38
Missing	3	3		
Breastfeeding/expressing at time of interview	10 (60.0)	12 (68.4)	1.00† (0.23–4.28)	1.00
Stopped breastfeeding	5 (40.0)	6 (31.6)		
Missing	2	1		
Duration of breastfeeding (days), median (25th–75th centile)	37 (0–46)	43 (0.5–60)	0.94§ (0.39–2.28)	0.89

fibrinogen replacement. Future studies will need to consider strategies to ensure inclusion of all eligible patients.

Fibrinogen concentrate rather than cryoprecipitate was used because it could be mixed and given within 10 min and allowed the intervention to be blinded.[22] Fibtem A5 was used to facilitate early infusion of fibrinogen concentrate. Our study supports the feasibility of managing severe obstetric haemorrhage using Fibtem but does not address cost effectiveness.

All women received prophylactic tranexamic acid; the effect of fibrinogen concentrate in the absence of this drug is

Table 4 Estimated treatment effect on outcomes by pre-specified subgroups. *Incidence rate ratio (IRR) of the fibrinogen arm compared with the placebo arm. An IRR <1 indicating more transfusions in the placebo arm and an IRR >1 indicating more transfusions in the fibrinogen arm. †Data were transformed before modelling using log plus one transformation. The stated *P*-value is associated with the interaction test. If the interaction test is not significant, there is no evidence that the treatment effects in each subgroup are significantly different from each other. Caesarean section and platelet count at the time of randomization had no effect on these study outcomes

	Fibrinogen (*n*=28)	Placebo (*n*=27)	Unadjusted treatment effect estimate (95% CI)	Interaction term *P*-value
Total allogeneic blood products after study medication until discharge, units				
Fibtem A5 at randomization				
≤12 mm	*n*=13	*n*=15		
Median (25th–75th centile)	1.0 (0.0–4.5)	3.0 (0.0–6.0)	0.59* (0.19–1.84)	
>12 mm	*n*=15	*n*=12		0.135
Median (25th–75th centile)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	2.13* (0.64–7.06)	
Missing	0	0		
Fibrinogen at randomization				
<2 g litre^{-1}	*n*=3	*n*=4		
Median (range)	1.0 (1.0–15.0)	7.0 (3.0–23.0)	0.57* (0.14–2.36)	
≥2 g litre^{-1}	*n*=21	*n*=18		0.458
Median (range)	0.0 (0.0–8.0)	0.0 (0.0–6.0)	1.31* (0.44–3.92)	
Missing	4	5		
Measured abnormal blood loss 24 h after study medication (ml)				
Fibtem A5 at randomization				
≤12 mm	*n*=13	*n*=15		
Median (25th–75th centile)	300 (100–350)	700 (200–1550)	−1.04† (−2.17 to 0.08)	
>12 mm	*n*=15	*n*=12		0.078
Median (25th–75th centile)	200 (55–355)	155 (1.25–525)	0.81† (−0.94 to 2.56)	
Fibrinogen at randomization				
<2 g litre^{-1}	*n*=3	*n*=4		
Median (range)	300 (100–745)	1770 (700–3000)	−1.73† (−2.73 to − 0.73)	
≥2 g litre^{-1}	*n*=21	*n*=18		0.329
Median (range)	200 (0–1465)	230 (0–1700)	−0.14† (−1.47 to 1.19)	
Missing	4	5		
Time in level 2/3 care (h)				
Fibtem A5 at randomization				
≤12 mm	*n*=13	*n*=15		
Median (25th–75th centile)	15 (9.25–26.5)	22 (10.0–29.0)	0.19† (−0.63 to 1.01)	0.850
>12 mm	*n*=15	*n*=12		
Median (25th–75th centile)	16.0 (13.0–25.0)	16.5 (8.0–26.75)	0.29† (−0.43 to 1.02)	
Fibrinogen at randomization				
<2 g litre^{-1}	*n*=3	*n*=4		
Median (range)	15 (10–320)	30 (1.5–74)	0.36† (−0.91 to 1.63)	
				0.402
≥2 g litre^{-1}	*n*=21	*n*=18		
Median (range)	15 (2–20)	18 (0–88)	0.005† (−0.56 to 0.57)	

unknown. No significant safety issues were raised although the study was not powered to detect these. There were two thrombotic events, one in each of the placebo and fibrinogen groups.

In conclusion, infusion of fibrinogen concentrate triggered by Fibtem A5 ≤15 mm did not improve outcomes. Subgroup analyses suggest that fibrinogen replacement is not required if Fibtem is >12 mm or fibrinogen is >2–2.5 g litre^{-1}, but an effect below those levels cannot be excluded. Studies are required that randomize women to fibrinogen replacement with Fibtem/fibrinogen <12 mm/2.5 g litre^{-1} to investigate whether this is clinically and cost effective.

Authors' contributions

Study design, data interpretation, data analysis and writing the first draft of the manuscript: P.W.C.

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Study conduct and governance, oversight of data integrity, data interpretation and critical revision of manuscript: N.A., J.T.

Study design and sample size calculation, oversight of study conduct and governance, oversight of data analysis, data interpretation and critical revision of manuscript: K.H.

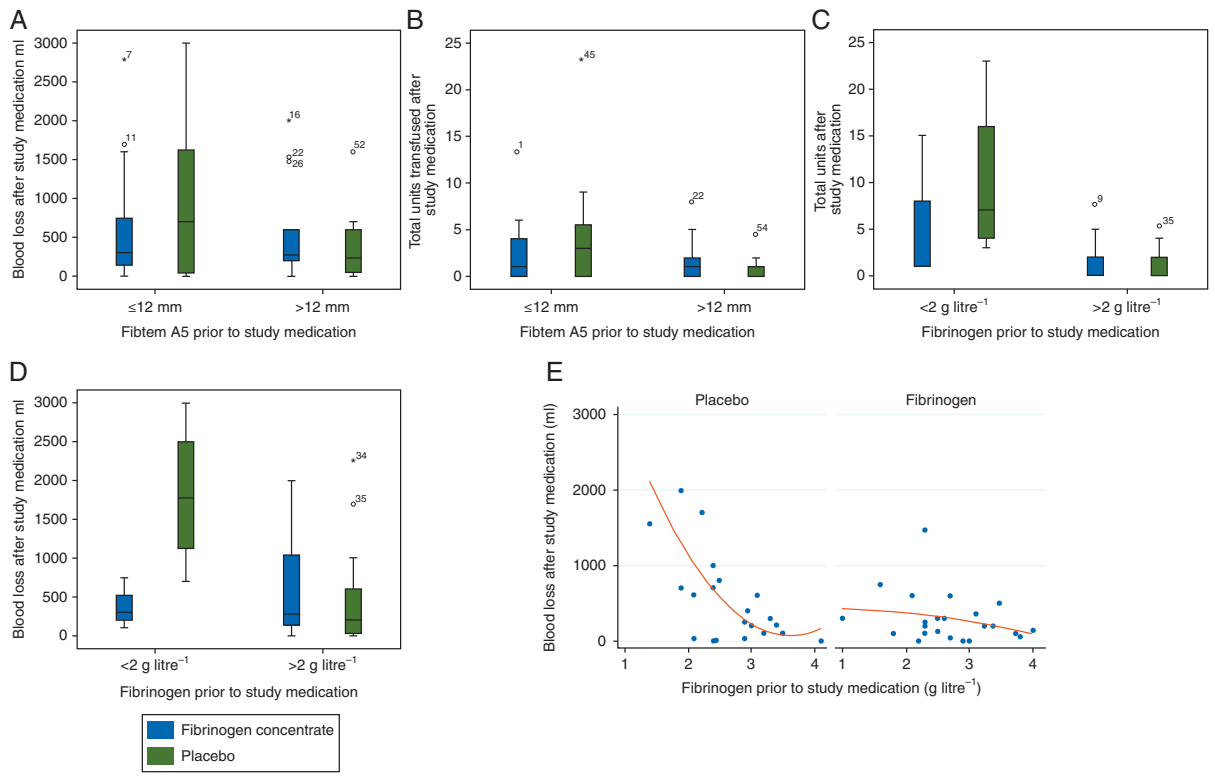

Fig 2 Effect of Fibtem A5 and fibrinogen level at the time of randomization on transfusion and blood loss after study medication.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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